In-utero exposure to breast cancer treatment: a population-based perinatal outcome study.

Running title:

In-utero exposure to breast cancer treatment

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Abstract

Chemotherapy during a viable pregnancy may be associated with adverse perinatal outcomes. We conducted a prospective cohort study to examine the perinatal outcomes of babies born following in-utero exposure to chemotherapy in Australia and New Zealand. Over 18 months we identified 24 births, of >400g and/or >20-weeks gestation to women diagnosed with breast cancer in the first or second trimesters. Eighteen babies were exposed in-utero to chemotherapy. Chemotherapy commenced at a median of 20 weeks gestation, for a mean duration of 10 weeks. Twelve exposed infants were born preterm with 11 by induced labour or pre-labour caesarean section. There were no perinatal deaths or congenital malformations. Our findings show that breast cancer diagnosed during mid-pregnancy is often treated with chemotherapy. Other than induced preterm births, there were no serious adverse perinatal outcomes.

Background:

The management of cancer diagnosed during pregnancy poses unique challenges in optimising maternal and infant outcomes. One of these challenges is choosing the optimal treatment regimen to balance the benefit to the women and the potential risks of adverse outcomes for the fetus[1]. Timing of treatment initiation is also challenging, especially if cancer diagnosis is early in the first trimester as fetal exposure to chemotherapy during the period of organogenesis has been associated with an increased risk of congenital malformations[2,3].

This study describes the perinatal outcomes of babies of women diagnosed with breast cancer during the first or second trimesters of pregnancy by whether exposed to in-utero systemic chemotherapy or not.

Methods:

A population-based prospective cohort study design was conducted in Australia and New Zealand using the Australasian Maternity Outcomes Surveillance System (AMOSS)[4]. We identified babies born to women with a confirmed diagnosis of breast cancer during pregnancy through monthly surveillance between January 2013 and June 2014. Eligible births included live or stillborn babies of at least 400 grams or 20 weeks gestation whether exposed to chemotherapy or not. Data were collected on maternal and cancer care, and perinatal outcomes.

Perinatal outcomes included: stillbirth, neonatal death, major congenital malformations, preterm birth (< 37 completed weeks of gestation), low birthweight (< 2,500 grams) and small for gestational age (birthweight < 10^{th} percentile for gestational age)[5].

Chi-square, Fisher's exact test, Fisher-Freeman-Halton test, and independent sample t-test were used to investigate the difference in outcomes of babies stratified by in-utero exposure to chemotherapy.

Results

Of the 24 babies born to women diagnosed with breast cancer during the 1st and 2nd trimesters of pregnancy, 18 (75%) were exposed to chemotherapy, and six were not (detailed in Supplementary Table 1). Demographic and treatment characteristics of the 24 women are shown in Supplementary Tables 1 & 2.

The types of systemic chemotherapeutic agents used during the pregnancies are listed in Supplementary Table 3. The median gestational age at first in-utero exposure was 20 weeks (range 13 - 31). Fourteen (77.8%) of the 18 babies had their first exposure in the second trimester and four (22.2%) in the third trimester. All 18 babies were exposed to a minimum of two therapeutic agents with a mean duration of exposure of 10.4 ± 5.8 weeks. All babies were exposed to alkylating agents; either nitrogen mustard (Cyclophosphamide) or platinum compounds (Carboplatin), 16 (88.9%) were exposed to anthracyclines (Doxorubicin or Epirubicin), 10 (55.6%) to taxanes (Paclitaxel or Docetaxel) and 1 (5.6%) to Fluorouracil.

The mean gestational age at birth for the 18 chemotherapy exposed babies was 35.7 ± 2 weeks, significantly lower than that for the six non-exposed babies (mean 38.8 ± 1.5 weeks) (P =0.002) (Table 1). There were no stillbirths, diagnosed congenital malformations or neonatal deaths in any of the 24 babies. The need for resuscitation was seen in the two babies exposed to Tamoxifen combined systemic therapy (Cyclophosphamide, Doxorubicin and Docetaxel and Tamoxifen; and Paclitaxel, Carboplatin and Tamoxifen). The former was female born following induction at 36 weeks, birthweight 2480 grams Apgar score at 5 minutes of 8 and resuscitated

with a continuous positive airway pressure (CPAP) mask, however, discharged home without the need for admission to neonatal intensive care (NICU) or Special Care Nursery (SCN).

The latter was male delivered at 34 weeks by CS (birthweight 2240 grams, Apgar score at 5 minutes of 8) and required resuscitation with a continuous positive airway pressure (CPAP) mask and admission to the SCN.

A third baby exposed to Trastuzumab, Docetaxel and Cyclophosphamide was born vaginally following induction at 36 weeks (birthweigh 2380 grams; Apgar score of 10) and was admitted to SCN with mild respiratory distress before being discharged home on day 4.

Ten of the babies were exposed to Taxanes in addition to other chemotherapeutic agents. However, their perinatal outcomes did not significantly differ from those who had exposed to non-Taxane chemotherapy (Supplementary Table 4).

Discussion:

In this analysis, we examined the effect of in-utero exposure to chemotherapy on perinatal outcomes. As expected, the gestation at diagnosis influenced the decision on the timing of chemotherapy and the non-use of radiotherapy during pregnancy. All cases in our study whether exposed to chemotherapy or not were diagnosed in the first or second trimesters. The other factors influencing management decisions are the grading and staging of breast cancer. Of note, none of the non-exposed babies' mothers had distant metastasis and none had a preterm birth.

It is recognised that management decisions are often a delicate balance in considering the treatment impacts on both the maternal and fetal health during the pregnancy. In this study, apart from preterm birth, there were no serious adverse perinatal outcomes in the 18 babies

exposed to chemotherapy nor in the six non-exposed babies. There was no perinatal death or congenital malformations.

The majority of exposed babies were exposed to cyclophosphamide and doxorubicin, with one baby exposed to trastuzumab and two others to tamoxifen. This is consistent with the other studies in which the babies were mainly exposed to a combination of cyclophosphamide and doxorubicin[6-9].

Tamoxifen is contraindicated during pregnancy[10]. The two babies who were exposed to tamoxifen in our study were born without congenital malformations. However, due to the small number of babies exposed to tamoxifen in our study, we were unable to recommend the use of tamoxifen during pregnancy.

Trastuzumab is contraindicated during pregnancy, as it has been associated with oligohydramnios and renal impairment in the fetus[11]. We were unable to confirm this association as in our study only one baby was exposed to trastuzumab in the third trimester.

In agreement with other studies[2], our results show a significantly higher rate of preterm births among babies exposed to systemic therapy during pregnancy compared to the non-exposed babies (12 out of 18 vs 0 out of 6).

Morbidities in neonates (low birthweight and admission to NICU/SCN) in our study were directly linked to preterm birth. Similar to the previous studies[2,9], the leading cause of preterm birth amongst the exposed group in our study is iatrogenic to facilitate maternal systemic chemotherapy postpartum (supplementary figure 1).

There is growing evidence on the safety of exposure to anthracyclines containing regimens after the first trimester; however, it is limited for the other chemotherapeutic agents and the

non-chemotherapy systemic treatment. There is a need for standardised information on the maternal-fetal exposure and outcomes of chemotherapy and other systemic anticancer agents use in pregnancy that is collated internationally into a database for use in informing clinical practice and research worldwide.

A major strength of this cohort study is its population-design of all cases in Australia and New Zealand during the study period. Limitations include the rarity of the condition, the low uptake of chemotherapy during pregnancy and the follow-up period being restricted to the perinatal period.

Conclusion:

Our study provides assurance that there were no congenital abnormalities or perinatal deaths among the 18 babies exposed to at least two different chemotherapy agents during pregnancy. The directionality of our findings is consistent with the two largest studies in the international literature, particularly regarding preterm birth[6,7]. Larger observational studies are needed to provide better information on in-utero exposure and outcomes following chemotherapy to inform gestational breast cancer management.

Additional Information:

- Ethics approval and consent to participate:

  Ethics approval for our study was granted by the NSW Population and Health Services Research Ethics Committee (HREC/09/CIPHS/21), and multiple Human Research Ethics Committees across Australia. Multi-Regional Ethics Committee approval (MEC/09/73/EXP) was granted in New Zealand.
- Consent for publication: NA

- Availability of data and material: data will be available from the corresponding author on reasonable request.
- Conflict of interest: the authors declare no conflict of interest.
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- Authors' contributions: all authors were involved in the conception and design of the study and data interpretation. NS drafted the manuscript and performed data analysis. AW, ZL were involved in the data analysis and NS, AW, ZL and ES in data interpretation. All authors critically revised the manuscript and approved it for submission.
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Table 1: Perinatal outcomes amongst the 24 babies.

	Exposed (n=18)	Non-exposed (n=6)	P value
Live births	18(100)	6(100)	NA
Neonatal deaths*	0(0)	0(0)	NA
Preterm (<37 weeks)			
Yes	12(66.7)	0(0)	
<32 weeks	*1(5.6)*	*0(0)*	0.014
33-<37 weeks	*11(61.1)*	*0(0)*	
No	6(33.3)	6(100)	
Small for gestational age	2(11.1)	0(0)	1.000
Low birthweight (<2500 g)	9(50)	0(0)	0.052
Resuscitation			
Yes	6(33.3)	0(0)	
Neopuff or CPAP mask only	*3(16.7)*	*0(0)*	
Oxygen	*1(5.6)*	*0(0)*	0.277
Neopuff or CPAP mask + Suction + Oxygen	*2(11.1)*	*0(0)*	
No	12(66.7)	6(100)	
Respiratory support			
Yes**	1(5.6)	0(0)	1.000
No	16(88.9)	6(100)	
Not known	1(5.6)	0(0)	
Apgar score (5 minutes)			
8	5(27.8)	0(0)	
9	10(55.6)	5(83.3)	0.348
10	3(16.7)	1(16.7)	
Admission to NICU/SCN	9(50)	1(16.7)	0.341
Breastfeeding initiated			
Yes	6(33.3)	5(83.3)	0.061
No	12(66.7)	1(16.7)	

*During hospital stay only, **CPAP mask only.

Supplementary Table 1: Maternal demographics

	Exposed (n=18)	Non-exposed (n=6)	P value
Country			
Australia	15(83.3)	5(83.3)	1.000
New Zealand	3(16.7)	1(16.7)	
Age (years)			
<35	9(50)	3(50)	1.000
≥35	9(50)	3(50)	
BMI (kg/m^2)			
18.50 - 24.99	12(66.7)	4(66.7)	1.000
≥25.00	5(27.8)	2(33.3)	
Unknown	1(5.6)	0(0)	
Hospital Sector			
Public	11(61.1)	5(83.3)	0.621
Private	7(38.9)	1(16.7)	
Parity			
0	7(38.9)	4(66.7)	0.357
≥1	11(61.1)	2(33.3)	
Smoking status			
Never smoked	9(50)	5(83.3)	
Quit smoking before becoming pregnant	4(22.2)	0(0)	0.319
Smoking during pregnancy	1(5.6)	1(16.7)	
Not known	4(22.2)	0(0)	
ART*			
Yes	0(0)	0(0)	N/A
No	18(100)	5(83.3)	
Not known	0(0)	1(16.7)	

*ART = assisted reproductive technology

Supplementary Table 2: Maternal cancer characteristics, tumour treatment and obstetric management

	Exposed (n=18)	Non-exposed (n=6)	P value
Tumour grade			
Low	0(0)	3(50)	
Intermediate	3(16.7)	0(0)	0.030
High	12(66.7)	3(50)	
Not known	3(16.7)	0(0)	
Lymphovascular Involvement			
Yes	7(38.9)	0(0)	0.123
No	9(50)	5(83.3)	
Not known	2(11.1)	1(16.7)	
Estrogen receptor status			
Positive	12(66.7)	4(66.7)	1.000
Negative	5(27.8)	1(16.7)	
Not known	1(5.6)	1(16.7)	
Progestrone receptor status			
Positive	9(50)	4(66.7)	
Negative	8(44.4)	1(16.7)	0.360
Not known	1(5.6)	1(16.7)	
HER 2 status			
Positive	4(22.2)	0(0)	0.546
Negative	13(72.2)	4(66.7)	
Not known	1(5.6)	2(33.3)	
Metastatic Disease			
Yes	6(33.3)	0(0)	0.144
No	11(61.1)	6(100)	
Not known	1(5.6)	0(0)	
Surgery During Pregnancy			
Yes	15(83.3)	5(83.3)	1.000
No, delayed until end of pregnancy	3(16.7)	1(16.7)	
Radiotherapy During Pregnancy			
No, not recommended	6(33.3)	3(50)	0.635
No, delayed until end of pregnancy	12(66.7)	3(50)	
Postpartum Systemic Therapy			
Yes	17(94.4)	2(33.3)	0.021
No	1(5.6)	3(50)	
Not known	0(0)	1(16.7)	
Corticosteroid for fetal lung maturity			
Yes	10(55.6)	0(0)	0.015
No	6(33.3)	6(100)	
Not known	2(11.1)	0(0)	
Induction of labour			
Yes	10(55.6)	5(83.3)	0.531
No/not applicable	8(44.4)	1(16.7)	
Method of birth			
Vaginal birth	11(61.1)	4(66.6)	1.000
Caesarean section	7(38.9)	2(33.3)	

Supplementary Table 3: Systemic therapeutic agents during pregnancy.

	Timing of therapy		
	2nd Trimester (13-27 weeks) (n=14) n* (%)	3rd Trimester (28-40) weeks (n=4) n* (%)	Total (n=18) n* (%)
Cyclophosphamide			
Yes	13(92.9)	4(100)	17(94.4)
No	1(7.1)	0(0)	1(5.6)
Carboplatin			
Yes	1(7.1)	0(0)	1(5.6)
No	13(92.9)	4(100)	17(94.4)
Docetaxel			
Yes	2(14.3)	1(25)	3(16.7)
No	12(85.7)	2(50)	14(77.8)
Not stated	0(0)	1(25)	1(5.6)
Doxorubicin			
Yes	12(85.7)	3(75)	15(83.3)
No	2(14.3)	0(0)	2(11.1)
Not stated	0(0)	1(25)	1(5.6)
Epirubicin			
Yes	1(7.1)	0(0)	1(5.6)
No	13(92.9)	2(50)	15(83.3)
Not stated	0(0)	2(50)	2(11.1)
Fluorouracil			
Yes	1(7.1)	0(0)	1(5.6)
No	13(92.9)	2(50)	15(83.3)
Not stated	0(0)	2(50)	2(11.1)
Paclitaxel			
Yes	6(42.9)	1(25)	7(38.9)
No	8(57.1)	2(50)	10(55.6)
Not stated	0(0)	1(25)	1(5.6)
Tamoxifen			
Yes	2(14.3)	0(0)	2(11.1)
No	12(85.7)	2(50)	14(77.8)
Not stated	0(0)	2(50)	2(11.1)
Trastuzumab			
Yes	0(0)	1(25)	1(5.6)
No	14(100)	2(50)	16(88.9)
Not stated	0(0)	1(25)	1(5.6)

*Babies may have been exposed to more than one therapeutic agent.

Supplementary Table 4: Perinatal outcomes amongst the 18 babies exposed to chemotherapy based of their exposure to Taxanes.

	Taxanes yes (n=10)	Taxanes no (n=8)	P value
Live births	10(100)	8(100)	NA
Neonatal deaths*	0(0)	0(0)	NA
Preterm (<37 weeks)			
Yes	7(70)	5(62.5)	
<32 weeks	*0(0)*	*1(12.5)*	1.000
33-<37 weeks	*7(70)*	*4(50)*	
No	3(30)	3(37.5)	
Small for gestational age	1(10)	1(12.5)	1.000
Low birthweight (<2500 g)	(0)	(0)	1.000
Resuscitation			
Yes	4(40)	2(25)	
Neopuff or CPAP mask only	*2(20)*	*1(12.5)*	
Oxygen	*1(10)*	*0(0)*	1.000
Neopuff or CPAP mask + Suction + Oxygen	*1(10)*	*1(12.5)*	
No	6(60)	6(75)	
Respiratory support			
Yes**	1(10)	0(0)	1.000
No	9(90)	7(87.5)	
Not known	0(0)	1(12.5)	
Apgar score (5 minutes)			
8	3(30)	2(25)	
9	4(40)	6(75)	0.241
10	3(30)	0(0)	
Admission to NICU/SCN	5(50)	4(50)	1.000
Breastfeeding initiated			
Yes	3(30)	3(37.5)	1.000
No	7(70)	5(62.5)	

Supplementary Figure 1 Mode of birth and postpartum maternal treatment for preterm babies exposed to systemic therapy